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F.A.C.P., F.I.D.S.A.*

WAISBREN CLINIC
INNOVATIO SERVATIO SCHOLARIS
EST. 1951

INTERNAL MEDICINE
INFECTIOUS DISEASES
IMMUNOLOGY
IMMUNOMODULATION THERAPY

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CASE SUMMARY

OF ERIC JEFFRIES

This 38-year-old, successful, dynamic man was completely well until one week after he received an injection of recombinant hepatitis B vaccine in June of 1997. The family history revealed that one sister is said to have a positive ANA test. His father has retinitis pigmentosa. There was a remote family history of insulin-dependent diabetes. His past medical history was that he had a Rickettsial disease as a child and epididymitis treated successfully with antibiotics at age 33. He had had some nonspecific abdominal pain at age 34.

Mr Jeffries was not informed that serious reactions could be caused by hepatitis B vaccine. He had a moderate but definite sore throat the day before the injection. He had no risk factors for hepatitis B that had been documented by the CDC&P He was told that the vaccination might cause soreness of the upper arm He was asked to, and did, sign some form of consent but was not given a definitive answer by the nurse when he asked details about what and why he was signing. There was no discussion with his physician about the vaccine and its possible dangers.

One week after the vaccination he became acutely ill with severe headaches, profuse sweats, mental confusion and generalized joint and muscle aches. There was some immediate improvement after about a week, but the aforementioned symptoms had remained in varying degrees until the day of his

examination on September 14, 1999. He called SmithKline about the reaction and was told that he had a serum sickness type of reaction with which they were familiar.

During the ensuing 27 months he became completely disabled with an intermittent symptom complex that included in their order of their causing difficulties; cognition and memory difficulties of severe proportion, bone and muscle pain always present. He was prone for no apparent reason to severe exacerbations of abdominal pains, cognition and memory difficulties at about two monthly intervals. At the time that these exacerbations occurred he had severe chills, intensification of his bone and joint pains, and headaches. Interestingly, he has never had a fever. He has had, intermittently, a rash that was suggestive of vasculitis, a viral disease, or leukocytoblastic vasculitis. The rash has not been biopsied He had some aphthous ulcers which brought up the questions of Bechet's disease. In this regard, he saw a specialist who discounted the possibility.

As might be expected, he has had trials of prednisone with perhaps some relief but no definitive help There was a similar experience with methotrexate and the various nonsteroidal medications. On physical examination, I found only hyporeflexia with absent abdominal reflexes in the right upper quadrant Table 1 shows the diseases considered by various consultants and essentially ruled out. Table 2 summarizes the pertinent laboratory work. I have placed asterisks after those that might be consistent with autoimmunity.

Conclusion By exclusion of other diseases, by reports of similar situations in the literature, by experience with autoimmune diseases that have followed other viral vaccines (Swine flu), and by my personal experience with having seen other similar cases, I conclude that Mr. Jeffries is suffering from chronic debilitating postvaccinal encephalomyelitis and acquired autoimmunity.

Table I. Diseases considered and effectively ruled out by competent specialists over the past two years. Their reports and conclusions are available.

1. Porphyria.
2. Hepatitis.
3. Noninflammatory rheumatism.
4. Whipple's disease.
5. Ulcerative colitis.
6. Occult infection.
7. Bechet's syndrome.
8. Fibromyalgia.*
9. Gilbert's disease.*
10. Hemolytic anemia.
11. Cholecystitis.
12. Undifferentiated connective tissue disease.**
13. Epididymitis.*
14. Lupus erythematosus.*
15. Multiple sclerosis **
16. Hemochromatosis.
17. Paroxysmal nocturnal hemoglobulinuria.
18. Fatty liver *

* Astericks indicate diseases that may be present as part of the acquired autoimmunity syndrome.

Multiple sclerosis, in my opinion, is still in the picture and probably should be additionally ruled out by an MRI which includes the spine.

Table 2. Pertinent laboratory work.

1. Normal urine porphyries.
2. Fatty infiltration of the liver.
3. CAT scan of the abdomen.
4. GI series - Negative.
5. Barium enema - Negative.
6. Colonoscopy - Not diagnostic.
7. Tissue typing. A - 0301.2402

   B - 07021.0702 (I am not sure of the significance of these studies).
8. Auto antibodies to thyroxine.*
9. Borderline HLA-B27.*
10. Serum iron.
11. Serum ferritin.
12. Cold agglutinates *
13. CPK elevated *
14. Sedimentation rate.
15. Antinuclear antibodies.
16. C-reactive protein.
17. Joint x-rays
18. EMG
19. Thyroid studies *

* Asterisks indicate studies that may be important.

I included the thyroid studies in a negative way because if the auto antibodies against thyroid that were found may make the normal studies inaccurate.

Hypothetical explanation of the pathogenesis of Mr. Jeffries clinical condition. Background writings in this regard are appended.

The hepatitis B vaccine given to Mr. Jeffries either contained polypeptides that were identical or nearly identical to those present in his own tissues, or the vaccine contained polypeptides that were complimentary to a virus present in his own system (he had a positive titer against Epstein-Barr virus which should have shown homology with human tissues). Because he had a sore throat, there were also present in his body, antigens present in all bacterial cell walls muranyl peptides. These act as immunologic adjuvants. Mr. Jeffries also must have had a genetic make up that makes one susceptible to autoimmune diseases (HLA-B27 was reported once), (his sister also had a positive ANA). The proteins that are probably being affected by the autoimmunity are receptor sites in the brain and also myelin, nerve, muscle and joint substances

Thus we can hypothesize that the elements necessary to evoke a postvaccinial encephalomyelitis were present These include 1) Antigens that show homology with human tissue, either from the vaccine or from an accompanying virus. 2). An immunologic adjuvant - either from the muramyl peptides from the bacteria in the throat or aluminum in the vaccine. 3). Complementarity between the vaccine and the virus 4) A host with a tendency to autoimmunity because of a genetic pattern that made him susceptible to autoimmunity This concept was advanced by Westal and Root-Bernstein in 1985 to explain postvaccinal encephalomyelitis The reference is in several of the appended manuscripts.

Of course, this is only a working hypothesis to explain a syndrome which has been described since 1888 when one of Pasteur's first patients developed it. Based on this hypothesis, it seems reasonable to try to help this patient with an antiviral which will hopefully suppress the offending virus and with

gamma globulin which theoretically may help suppress the virus or may give natural blocking antibodies which will prevent attack of receptor sites in other body tissues. This is an unproven hypothesis, amenable to experimental proof of the type suggested by Kuhn and his classic work on medical hypotheses.

This hypothesis does not, at present, prove that Mr. Jeffries is totally disabled because of the vaccine. This assertion however, is supported beyond a reasonable medical doubt by ruling out of all other possible causes of the disability, by the medical literature and by the personal observations by myself of him and other similar patients.

Dictated by

Burton A. Waisbren, Sr., M.D

Statement of Burton A. Waisbren, Sr., M. D.

State of Wisconsin)
) **ss.**
County of _____)

I, Burton A. Waisbren, M.D., after being duly cautioned and sworn state the following on the basis of my own personal knowledge.

1. I am a physician and am licensed to practice medicine in the State of Wisconsin. My curriculum vitae is attached.

2. In September 1999, I saw Mr. Eric Jeffries for a malady which causes him to suffer myalgias, arthralgias, abdominal pains, severe headaches, malaise, and various other body aches.

3. I have diagnosed Mr. Jeffries' condition as chronic debilitating postvaccinal encephalomyelitis and acquired autoimmunity. My four page case summary of Mr. Jeffries' condition is attached.

4. The effects of Mr. Jeffries illness make him unable to perform the material and substantial duties of his occupation of a merchant banker.

Further Affiant Sayeth Naught.

Burton A. Waisbren, M. D.

Notary Public

Before me appeared Burton A. Waisbren, M. D., who after being duly cautioned and sworn, signed his name above.

_____

CURRICULUM VITAE-BURTON A. WAISBREN, SR., M.S., M.D., F.A.C.P.

Born in Shorewood, Wisconsin		1922
University of Wisconsin	B.S.	1944
University of Wisconsin	M.D.	1946
Interned, Boston City Hospital, Harverd Service		1946
Navy Service-Biological Warfare Center, Camp Dietrick, Maryland		1947
Navy Medical Research Institute, Bethesda, Maryland		1948
Residency-University of Minnesota		1950
Instructor in Medicine-University of Minnesota		1951
University of Minnesota (Genetics)	M.S.	1951
Director, Infectious Disease Control Laboratory, Milwaukee County Hospital		1951-1969
Assistant Clinical Professor of Medicine, Marquette Medical School		1952-1956
Central Society Clinical Research		1953-Present
Sigma Xi		1955-Present
Diplomate Internal Medicine		1956
Fellow American College of Physicians		1957
Associate Clinical Professor of Medicine, Medical College of Wisconsin		1960-1986
Medical Director and Internist, St. Mary's Hospital Burn Center		1961-1982
Infectious Disease Society of America, Founding Member		1963-Present
American Burn Association, Founding Member		1968-1986
Director, Burn Research and Clinical Paradigm Laboratory, St. Mary's Medical Center		1969-1982
International Society for Burn Injuries		1969-Present
Critical Care Society of America, Founding Member		1969-Present
Director, Immunotherapy Clinic, St. Mary's Medical Center		1974-1979
Member of Emergency Car Council, American Heart Association		1974-1981
Director and Founder, Junior Academy of Medicine		1974-1987
Critical Care Society of Wisconsin, Founding Member		1975-Present
Director, Clinical-Cell Biology Laboratory Mount Sinai Medical Center		1976-1979
Recertified by Examination, Internal Medicine		1978
Fellow of American Society of Infectious Diseases		1979
Director, Clin-path Cellular Biology Laboratory		1980-1982
Director, Clinical-Cell Biology Laboratory of Milwaukee, Incorporated		1986-1992
Alternate Delegate to State Medical Society		1987-Present
President, Infectious Disease Society of Milwaukee		1992

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Edited books published in Infectious Diseases and Internal Medicine
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Author of Systems Method of Critical Care, Three Editions.
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Author of Emergency Care for Patients.

Case Reports: Postvaccinal Encephalomyelitis Following Hepatitis B Vaccination.

Burton A. Waisbren, Sr., M.D., F.A.C.P.

Only that shall happen
which has happened.

Only that occurs
which has occurred.

There is nothing new beneath the sun!

Ecclesiastes 1.4

INTRODUCTION

The general acceptance of the concept of universal vaccination against hepatitis B, regardless of risk factors, makes it incumbent on physicians to be aware of the complications that have been reported to occur following the hepatitis B vaccination.[1-19] These complications have included a wide variety of reactions, most of which fit into an autoimmune category (3-19, Table 1). It is in this frame of reference that the two cases of postvaccinal encephalomyelitis seen by the author are being reported. A theoretic framework that might explain the pathogenesis of this complication and the studies suggested by this framework are discussed.

CASE REPORTS

Case 1

The patient is a 43-year-old female nurse who was in good health until August 1988. She had received two injections of hepatitis B vaccine in June 1988. Four weeks after the first vaccination, her husband noted that she began to have difficulty in concentrating and to have frequent severe headaches. She was taking a postgraduate course in nursing and contrary to her scholastic efforts in the past, she had difficulty in understanding and placing in context the relatively simple concepts that were being presented. In spite of headaches and cognition difficulties, she continued to work as a nurse. In October 1988 she developed a rash in her axilla which was nondescript in nature and which subsided in a month. She remained chronically ill with headaches, arthralgia and cognition defects, but she continued to try to work.

By mid-January 1989, her headaches had become too severe and she had to stop work. On January 19, 1989 her headaches increased even more in intensity and she became semiconscious. She was hospitalized and was in a deep coma for two weeks. No apparent cause of the coma was recognized and with supportive care, she gradually improved. Extensive studies in the hospital failed to definitely diagnose the etiology of her disease. They are summarized as follows: Cerebrospinal fluid studies showed 40 mononuclear cells, 79% were lymphocytes and 15% were monocytes. The sugar and protein content was normal. Serology studies of the cerebrospinal fluid that included studies for herpes simplex 1 and 2, measles, mumps, adenovirus, coxsackie virus, cytomegalovirus, herpes zoster and equine encephalitis were normal. Serum antinuclear antibodies were done three times. One showed a 1:40 titer of a speckled pattern, one showed a 1:80 titer of a homogeneous pattern, and the other was negative. The IgG titer against the Epstein-Barr virus was 1:160. Electrophoresis study of the cerebrospinal fluid was normal. A hepatitis B surface antibody test was positive. A Lyme test was positive with a fluorescent antibody titer of 1:512. Subsequent tests for Lyme antibodies were negative. A sedimentation rate was 4 mm/hr. A MRI of the brain and spinal cord was normal. A wide range of what might be called routine laboratory tests done on comatose patients was all normal. She was in the hospital for one month and diagnoses that were entertained, but not proven by the coterie of specialists who saw her were: Herpes meningitis, Lyme disease, and lupus erythematosus. She was discharged somewhat improved, but two weeks later she had to be readmitted to the hospital because of hypotension, weakness, anemia, low grade fever, joint pains and myalgia.

In April 1989, because her titer against the Borrelia antigen had been elevated, it was decided to treat her empirically for Lyme disease and she was given 2 grams of ceftriaxone IV for two weeks with no clinical response. She remained a semi-invalid with generalized weakness and mental confusion.

In August 1989, she developed slurred speech and a drooping right eye, so a course of IV penicillin was given, again, empirically for presumed chronic Lyme disease. There was no clinical response.

In November 1989, she noted difficulty with her sight and an ophthalmologist found optic neuritis. She continued to have fatigue, unsteadiness on her feet, visual problems, headaches, lack of concentration, generalized joint pains and weakness of her right arm and leg.

In January 1990, she was seen by myself. Based on the history of the two hepatitis B vaccine injections, the physical findings which included hyperactive knee and ankle reflexes, weakness of the right arm, absent abdominal reflexes, and the extensive negative studies that had been done, a diagnosis of postvaccinal encephalomyelitis and acquired autoimmune disease was made.

During the ensuing eight years the patient has noted gradual improvement in regard to fatigue and steadiness on her feet. She continues to have less mental activity than before and still has hyperreflexia, loss of visual acuity, absent abdominal reflexes and some weakness of her right arm and hand. In November 1997, a MRI of her brain failed to show any finding suggestive of multiple sclerosis. There has been no progression of symptoms.

Case 2

This 44-year-old female nurse received the hepatitis B vaccine in July 1988. Prior to this she had been extremely active and had no significant symptoms. Two weeks after the injection, she developed lethargy, joint pains and myalgia. The symptoms continued, but she continued to work until mid-September when she consulted a rheumatologist who found that she had an ANA titer of 1:500. He placed her on ten aspirins a day with no clinical response. In late December 1988, she had an episode at home in which she had a hazy sensorium and was semiconscious. An examination at an emergency room was nonrevealing except that a mitral prolapse was found and it was felt that it might have had a casual relationship to the event.

She continued to be chronically ill. In January 1989, a diagnosis of lupus erythematosus was made and she was started on chloroquine. Her ANA titer was markedly elevated at that time. There was no response clinically to the chloroquine sulfate. She continued to have headaches, lack of concentration, and unsteadiness on her feet and was unable to function in her profession.

On July 7, 1993, she lapsed into a deep coma, which lasted for one month. During a month in the hospital, she was only semiconscious and was incontinent. She was seen by numerous physicians and given an extensive medical work up. The presumptive diagnosis was lupus encephalomyelitis. A summary of significant laboratory results done in the hospital and subsequently is as follows: A brain biopsy was done which revealed thickened vascular walls surrounded by inflammatory cells. No evidence of a virus infection was seen. A culture of the brain tissue was negative for virus, bacterial, and fungal growth. The spinal fluid was sterile and acellular with normal protein and sugar concentrations.

A MRI showed scattered areas of increased signal in the brain stem and in both hemisphere and the thalamus. Serology studies showed high titers against herpes simplex, varicella zoster, rubeola and mumps. Serial studies for mycoplasma and Legionnaires disease were negative. There were antibodies against the hepatitis B surface antigen. Her IgG (2740 mg/dl), and IgA (490 mg/dl), were elevated, Compliment C4 was low at 9 mg/dl, ANA was 1:512, anti-DNA antibody was 1:512.

After a month in which there was no apparent result to therapy with prednisone it was decided to try a course of plasmapheresis (August 1993). She was plasmapheresed on three occasions. There was a definite response to this and she gradually regained full consciousness. As she came out of her coma, optic neuritis developed and she became blind in her right eye.

I first saw her and examined her records in March of 1994. At that time, she was being maintained on prednisone 20 mg per day, Prozac 20 mg and multiple vitamins. She had multiple joint pains, cognition difficulties, and chronic fatigue and had not regained the sight in her right eye. She had hyperactive knee and ankle reflexes, absent abdominal reflexes, balance problems, and still had cognitive difficulties.

When contacted in May of 1998, she stated that there was little change in her condition. Several neurologists have assured her after their examinations that she does not have multiple sclerosis. There has been no further evidence that she may have had lupus erythematosus.

DISCUSSION

The most likely diagnosis in both of these patients by exclusion and consideration of their course is postvaccinal encephalomyelitis.[20-23] There does not seem to be any other probable initiating factors that could be involved other then that the patients received hepatitis B vaccine.

The diagnosis of lupus erythematosus, which was considered in both of these cases, is untenable, in view of the fact that neither patient had enough major or minor criteria for the disease to make it an acceptable diagnosis.[24] The diagnosis of Lyme disease is equally untenable because of the lack of exposure and a characteristic skin rash in both cases and because Lyme titers have been shown to be present in other central nervous system diseases.[22,25,26] The fact that Lyme disease was suspected enough by consulting physicians to result in empirical treatment, suggests that other patients that have been diagnosed as having Lyme disease should be investigated to determine if they are actually suffering from acquired autoimmunity due to hepatitis B vaccine.

Other causes of chronic encephalomyelitis appear to have been ruled out by the numerous tests ordered by the many specialists who examined each patient. Thus, the prolonged course and residual findings in these cases best fit the clinical picture of postvaccinal encephalomyelitis, which has been described both after the sample rabies vaccine and the duck embryo vaccine.[20,21,22] The description that seems to best describe this condition is that of Dodson who defined it as "a diffuse interference with brain function resulting from a generalized or multifocal insult that causes a widespread disorder in the functions of neurons."[28]

If one accepts the diagnosis of postvaccinal encephalomyelitis as the etiology of these two cases, there is a wealth of animal experimentation regarding this condition to consider. This is because there is a generally accepted and extensively studied animal model of this condition.[29,30,31] It is called experimental allergic encephalomyelitis (EAE).[29,30,31] It has been postulated that the requirements specific of this experimental model are: Exposure of the animal to a group of polypeptide chains that are homologous or nearly homologous to its myelin, (molecular mimicry); simultaneous exposure of the animal to an antigen that exhibits complementarity to the antigen that exhibited molecular mimicry; simultaneous exposure to a immunologic adjuvant (usually derived from tubercle bacilli); possession of the animal of a characteristic lymphocyte antigen pattern.[31,32]

The EAE model suggests experiments that might explain the pathogenesis of postvaccinal encephalomyelitis as it occurs in humans. These experiments might also shed light on the broader field of acquired autoimmunity of the type reported to occur after hepatitis B vaccination. Viral antigens have already been shown to exhibit molecular mimicry with human myelin. [33] That suggests that viral vaccines can be studied for this characteristic. Patients who develop postvaccinal encephalomyelitis or any other form of autoimmunity after having received a vaccination can be studied to see whether they have been exposed to any bacterial or viral antigens that exhibit complementarity to the vaccine antigens.[31] They can also be studied to see if they have been exposed to bacterial cell walls, which might contribute to their immunologic spectrum. The most likely substances that would cause this are muramyl peptides, which are universal immunologic adjuvants.[34] Bacterial infections such as those caused by streptococci or mycoplasma come to mind in this respect. Finally, patients who develop

untoward vaccine reactions should have their HLA patterns determined to see if characteristic patterns surface.[15]

As interesting as the above theoretic considerations should be to basic scientists and developers of vaccines, the root reason for the presentation of these cases is to alert physicians that postvaccinal encephalomyelitis has occurred. Bayes in his seminal paper on statistics in 1761 pointed out that the probability that if something happens once, it will happen again.[35] The question remains as to how often this complication actually does occur. Certainly, it does not appear to occur often enough to discourage vaccination of individuals at high risk for acquiring hepatitis.[1] Whether it occurs often enough to discourage vaccination of low risk patients will only be known if clinicians are made aware of this possibility and if they report its occurrences. In the meantime, physicians will have to decide whether the possibility of acquired autoimmunity must be mentioned in the informed consent given to patients of low risk.

Table I: Seventeen articles that have appeared in the medical literature between 1983 through 1998 that suggest adverse reactions after vaccination against hepatitis B.

Reference	Journal	Suggested Adverse Reaction
3.	NEJM 1983; 309:614-15	Polyneuropathy
4.	Lancet 1987; 2:631-32	Uveitis
5.	AMJ Epid. 1988; 127:337-52	Guillain-Barre Syndrome
6.	Arch Int. Med 1988; 148:2685	Myesthemia Gravis
7.	NEJM 1989; 321:1198-99	Erythema Nodosum
8.	Inf. Dis. News 1992; 5:2	CNS Demyelination
9.	Lancet 1991; 338:1174-75	CNS Demyelination
10.	World Health Organization Adverse Drug Reaction Bulletin August 1990	Optic Neuritis
11.	J. Hepatol 1993; 19:317-8	Transverse Myelitis
12.	Clin. Infect. Dis. 1993; 17:928-29	CNS Demyelination
13.	BMJ 1990; 301:1281	Vasculitis
14.	Lancet 1993; 342:563-4	Visual Loss
15.	J. Neurol Neurosurg Psychiatry 1995 ; 58:758-59	CNS Demyelination
16.	Br. J. Rheumatol 1994; 33:991	Rheumatoid Arthritis
17.	BMJ 1994; 309:94	Reiter Syndrome and Arthritis
18.	Lancet 1988; 351:637-41	Autism & Colitis
19.	JAMA 1997; 278:1176-78	Hair Loss

REFERENCES

1. Kane, MA, Alter MJ, Hadler SC, Margolis HS. Hepatitis B infection in the United States. Recent trends and future strategies for control. Am J Med 1989; 87:11S-13S.

2. Hepatitis B virus: A comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination: Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1991; 40:RR-13, 1-25.

3. Ribera EF, Dutka AJ. Polyneuropathy associated with administration of hepatitis B vaccine (letter). N Engl J Med 1983; 309:614-15.

4. Fried M, Conen D, Conzelmann M., Steinemann E. Uveitis after hepatitis B vaccination (letter). Lancet 1987; 2:631-32.

5. Shaw FE Jr, Graham DJ, Guess HA, et al. Post-marketing surveillance for neurologic adverse events reported after hepatitis B vaccination. Experience of the first three years. AM J Epidimiol 1988; 127:337-52.

6. Biron P, Montpetit P, Infante-Rivard C, Lery L. Myasthenia gravis after general anesthesia and hepatitis B vaccine. Arch Intern Med 1988; 148:2685.

7. Goolsby PL. Erythema nodosum after Recombivax HB hepatitis B vaccine. N Engl J Med 1989; 321:1198-99.

8. Waisbren BA. Other side of the coin (letter). Inf Dis News 1992; 5:2.

9. Herroelen L, de Keyser J, Ebinger G. Central nervous system demyelination after immunization with recombinant hepatitis B vaccine. Lancet 1991; 338:1174-75.

10. Anonymous. Hepatitis B vaccines: reported reactions. World Health Organization Adverse Drug Reaction Bulletin. August 1990.

11. Trevisani F, Gattinara GC, Caraceni P, et al. Transverse myelitis following hepatitis B vaccination. J Hepatol 1993; 19:317-18.

12. Nadler JP. Multiple sclerosis and hepatitis B vaccination. Clin Infect Dis 1993; 17:928-29.

13. Cockwell P, Allen MB, Page R. Vasculitis related to hepatitis B vaccine. BMJ 1990; 301:1281.

14. Brezin A, Lautier-Frau M, Hamedani M, et al. Visual loss and eosinophilia after recombinant hepatitis B vaccine. Lancet 1993; 342:563-4.

15. Kaplanski G, Retornaz F, Durand J, Soubeyrand J. Central nervous system demyelination after vaccination against hepatitis B and HLA haplotype. J Neurol Neurosurg Psychiatry 1995; 58:758-59.

16. Vautier G, Carty JE. Acute sero-positive rheumatoid arthritis occurring after hepatitis vaccination. Br J Rheumatol 1994; 33:991.

17. Hassan W, Oldham R. Reiter's syndrome and reactive arthritis in health care workers after vaccination. BMJ 1994; 309:94.

18. Wakefield AJ, Murch SH, Anthony A, et al. Ileal - lymphoid hyperplasia, nonspecific colitis, and pervasive developmental disorder in children. Lancet 1998; 351:637-41.

19. Wise RP, Kiminyok P, Salive ME et al Hair loss after routine immunizations. JAMA 1997; 278:1176-78.

20. Label LS, Batts DH. Transverse myelitis caused by duck embryo vaccine arch. Neurol. 1982; 34:426-36.

21. Swamy H.s., Anisya V, Nandi SS, Kaliaperumd VG. Neurological complications due to Semple - type antirabies vaccine - clinical and therapeutic aspects. J Assoc Physicians India 1991; 39:667-669.

22. Stuart G, Krikorian KS. The neuroparalytic accidents of antirabies treatment. Ann Trop. Med. 1928; 23:327-377. (This article refers to the early literature in foreign languages).

23. Poser CM. Postvaccinal encephalitis (Letter). Ann Neurology 1983; 13:341-2.

24. Tan EM, Cohen AS, Fries JF et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1982; 25:1271-7.

25. Waisbren B.A., Cashman N, Schell RF, Johnson R. Borrelia Burgdorferi antibodies and amyotrophic lateral sclerosis. Lancet 1987; 2:332-3.

26. Garcia-Monco JC, Coleman JL, and Benach JL. Antibodies to myelitis basic protein in Lyme disease. Ji. of Inf. Dis. 1988; 158:667-668.

27. Schmutzhard E, Pohl P, & Stanek G. Borrelia Burgdorferi antibodies in patients with relapsing/remitting form and chronic progressive form of multiple sclerosis. J Neurol Neurosurg Psychiatry. 1988; 5:1215-1218.

28. Dodson WE, Metabolic encephalopathies in neurologic pathophysiology in: Eliason SG, Prensky AL, Hardin WB Jr. Ed. 1978. Neurological pathophysiology. New York, Oxford 1978.

29. Rivers JM & Schwentker. Encephalomyelitis accompanied by myelitis distraction experimentally produced in monkeys. J Exp. Med 1935; 61:689-702.

30. Shaw CM, Alvord FC. Adjuvant - antigen relationship in the production of experimental allergic encephalomyelitis in the guinea pig. J Exp. Med. 1962; 115:169-179.

31. Westall FC, Root-Bernstein RS. An explanation of prevention and suppression of experimental allergic encephalomyelitis. Mol. Immunol 1983; 2:169-177.

32. Root-Bernstein RS, Multiple-antigen-mediated autoimmunity (MAMA) in AIDS: a possible model for post-infectious autoimmune complications. Res Immunol 1990; 141:321-339.

33. Fujinami RS, Oldstone MB. Amino acid homology between the encephalitogenic site of myelin basic protein and virus. Mechanism for autoimmunity. Science 1985; 230:1043-45.

34. Hazenberg MP, de Visser H. Assay for n-acetyluramyl-L-alanine amidase in serum by determination of muramic acid released from the peptidoglycan of Brevibacterium divericatum. Eu J Clin Chem Biochem 1992; 30:141-44.

35. Bayes T. An essay towards solving a problem in the Doctrine of Chance 56. Reprinted in Biometrika 1985; 45:296-315.

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Summary of findings of a complete examination done in this office on September 22, 1999.

This 39-year-old stable health worker had hepatitis B at age 19. It was proven serologically but had a relatively benign course. She was essentially well until 8/11/95, when after receiving a second dose of hepatitis B vaccine, she developed severe pain and swelling at the bottom of her left foot which soon spread to the right foot and her ankles. The pain continued and included chronic muscle and joint aches, burning numbness, and tingling. Included with her symptoms has been severe muscle and joint pain, plus peripheral pain, extreme weakness, chills, personality changes, and difficulties in cognition. All of these symptoms have continued and she has been on intradermal narcotics in the past year. She has been to upwards of twenty physicians with no definitive diagnosis being offered. Studies did reveal exposure to hepatitis C are antigen and a liver biopsy at the Mayo Clinic was said to be slightly abnormal. This was done several years ago. In May of 1998, she developed a lymph node in her arm which biopsied as sarcoidosis. There were pulmonary findings as well which apparently resolved with treatment with corticosteriods. She has, in addition to antibodies to Hepatitis C, a positive rheumatoid factor. Nerve conduction studies indicated hyposensitivity which would be consistent with chronic Guillian-Barre disease. The family had a strong history of autoimmune disease with Addison's disease and diabetes. At present, there does not appear to be any outward drug and behavioral problems. Complete physical examination was normal except for some possible muscle weakness in the upper extremities.

I believe that [redacted] suffers from <u>postvaccinal generalized autoimmunity</u>. Her central nervous system, peripheral nervous system, joints, muscles, and cerebrum seem to be involved.

A treatment program was proposed in which sequentially rational methods that may help autoimmunity will be tried. We will start with an antiviral and gamma globulin, and if necessary, proceed to other, perhaps more theoretical approaches. These will include corticosteriods immune depressants (methyltrexate), leukophoresis, and generalized immune readjustments with combined immunotherapy (BCG, mixed bacteria vaccine, transfer factor, lymphoblastoid lymphocytes).

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Discussion was held with the patient and family regarding coping mechanisms. They were 1) Denial - never talk about, read about , or complain about disease to anyone but a counsellor to whom she should pour out her heart weekly, 2) Respect her limitations and do not push beyond them, 3)Get off narcotics. She will be seen in six weeks for evaluation of her progress.

There is no doubt in my mind that this is a vaccine related illness, based on my personal observations, the medieval literature, and many similar cases reported to VAERS. The question of hepatitis C will have to be addressed. This is being done by seeing if she has a "viral load" of this virus circulating in her blood.

The Theoretical Basis For the Approach Being Proposed

Post-vaccinal encephalomyelitis and autoimmunity is caused by what has been termed Multiple Antigenic Mediated Autoimmunity (the MAMA syndrome). The criteria for this syndrome are molecular mimicry between the host protein and one or the other of two complimentary antigens, genetic predisposition of the host, and the presence of an immune adjuvant. The core antigen of hepatitis B virus does demonstrate this and the capsular antigen from which the vaccine is made may also exhibit this. If the vaccine does not exhibit molecular mimicry, the virus complimentary to it might do this. A herpes virus would be the best candidate since these viruses do exhibit molecular mimicry with human myelin. The patient's family history suggests an HLA pattern consistent with both cases to autoimmunity. We know a immunologic adjuvant is present because aluminum, a time honored adjuvant, is present in the vaccine.

The theoretical approaches to the MAMA Syndrome are - treat the complimentary virus (valtrex), give Gama Globulin for blocking antibodies, use immunodepressants (methyltrexate), remove offending T-cells and auto antibodies (leukophoresis and plasmophoresis). The tests that might support this hypothesis are to determine if the vaccine is complimentary to the virus present as determined by serologic testing, to determine if molecular mimicry exists between the vaccine and human tissue, and to determine the patient's HLA pattern.